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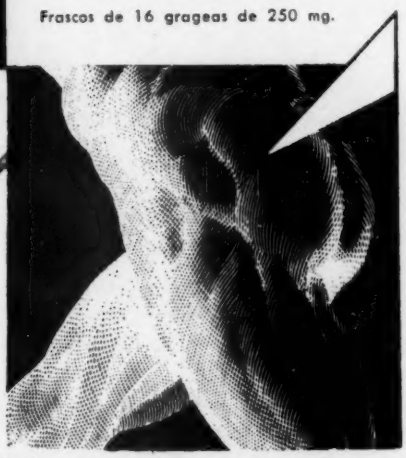

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THE ANTIDIURETIC POTENCY OF PREGNANT WOMEN SERUM

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THE ABILITY of women's blood serum to inactivate the antidiuretic principle of the posterior lobe of the hypophysis increases progressively during pregnancy. This antidiuretase activity, together with the oxytocinase potency, reaches its maximum during the last weeks before parturition (Croxatto et al. 1953). The considerable increase of this enzymatic activity, which destroys neurohypophyseal hormones, raises the question of why no signs of deficit of these hormones appear during pregnancy.

It could be supposed that in pregnant women the production of hormones increases to such a level, that the higher ability of plasma to inactivate them would be compensated. In order to clarify this problem we investigated comparatively: a) the antidiuretic potency of pregnant (9th month) and non pregnant women sera, and b) the inactivation of the antidiuretic activity of both sera, after incubation at 37°C.

MATERIAL AND METHODS

As experimental material sera samples of 25 women who were at the 9th month of pregnancy and were considered clinically normal, were used. The extracted blood was centrifuged immediately after coagulation. The serum obtained was divided in two equal parts: One was kept at low temperature (-3°C) until the moment of its assay; the other part was heated at 37°C during 4 or 8 hours, according to the experiments. Some drops of toluol were added to each sample as antiseptic. The same number of samples of normal non pregnant women serum received equal treatment simultaneously. After 4 or 8 hours of incubation the antidiuretic potency of both — incubated and kept at low temperature — samples of pregnant and non pregnant serum were tested. For this purpose the Burn test (1931), which has been employed in the course of former

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experiments, was used. 1 ml of serum was injected to each rat intraperitoneally. They received an average of 0.66 to 0.67 ml of serum per 100 grams weight. Every sample was injected to a group of 4 rats, immediately after hyperhydration. The urine excreted by each group was measured at intervals of 15 minutes during 3 hours, expressing the results as percentage of water eliminated with relation to the amount given previously. The effect of dialysis was tested on the remaining sera,

TABLE I

Antidiuretic effect of pregnant and non pregnant serum (25). Percentage of urinary excretion - Burn test

	60'		120'		180'	
Pregnant	8.7 ±2.1	2.9**	27.4±3.0	3.8	37.8±3.6	2.8
Non pregnant	18.3±2.5		44.5±3.4		52.0±3.6	
Pregnant inc. 4 h.	19.8±4.0	2.3	38.5±4.5	3.2	44.7±5.1	2.5
Non preg. inc. 4 h.	31.6±3.4		54.8±3.6		61.3±4.4	
Pregnant inc. 8 h.	39.2±8.4	1.0	57.5±5.3	1.3	79.5±2.7	0.5
Non preg. inc. 8 h.	51.0±8.1		68.1±5.9		82.2±6.5	
Pregnant dyaliz.	43.8±5.0	1.5	71.0±5.1	0.3	78.6±5.5	0.1
Non preg. dyaliz.	54.0±4.5		73.3±3.8		77.6±6.6	
Control	55.8±3.4		74.8±2.6		82.9±2.5	

* = Stand. Deviation
** = Sig Difference

which was kept at low temperature several days. A suitable volume of each sample was separated and, after measuring, was put into small cellulose tubes and dialyzed against current water for 24 hours. Antidiuretic activity of dialyzed and non dialyzed samples was studied by means of the same Burn test. Precaution was taken to determine previously the change of volume of the dialyzed sample in order to inject an equivalent of 1 ml of non dialyzed serum.

RESULTS

Table I and figure 1 show that the antidiuretic potency of pregnant women serum is significantly higher than that of the non pregnant. Incubation at 37°C during 4 hours diminishes the antidiuretic potency of both sera, but the difference in favor of the pregnant sample is maintained, thus the decrease in the antidiuretic activity of both samples of blood is parallel. In spite of the decrease in the antidiuretic potency of the pregnant serum after 4 hours incubation, this activity is still slightly higher than that of non pregnant, non incubated serum.

Incubation of 8 hours destroys practically all the antidiuretic activity of the sera, while the inactivation is slightly greater in the sera from non pregnant women, a significant difference between them could not be established. Dialysis produced an almost complete disappearance of the antidiuretic potency of the sera, more marked in those from non pregnant women.

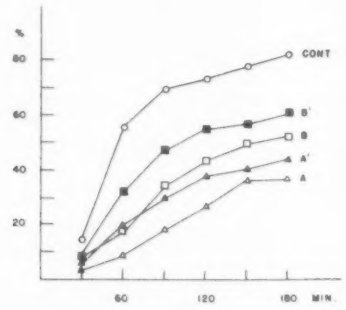

FIG. 1. — *Antidiuretic effect (Burn test). Each curve represents the mean value of 100 rats injected intraperitoneally with 1 ml of:*
A: *pregnant woman serum, kept at low temperature.*
A': *pregnant woman serum, kept at 37°C during 4 hours.*
B: *non pregnant woman serum, kept at low temperature.*
B': *non pregnant woman serum, kept at 37°C during 4 hours.*
Cont: *NaCl solution 0.9 per cent.*

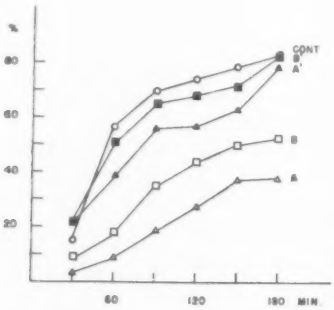

FIG. 2. — *Antidiuretic effect (Burn test) Each curve represents the mean value of 100 rats injected intraperitoneally with 1 ml of:*
A: *pregnant woman serum kept at low temperature.*
A': *pregnant woman serum, kept at 37°C during 8 hours.*
B: *non pregnant woman serum kept at low temperature.*
B': *non pregnant woman serum kept at 37°C during 8 hours.*
Cont.: NaCl solution 0.9 per cent.

The average urine excretion of animals injected with dialyzed samples was practically identical to that found after injection of samples incubated during 8 hours 37°C (Fig. 3).

Discussion

As a result of the above experiments, it is evident that the antidiuretic potency of pregnant women sera (9th month), as determined by

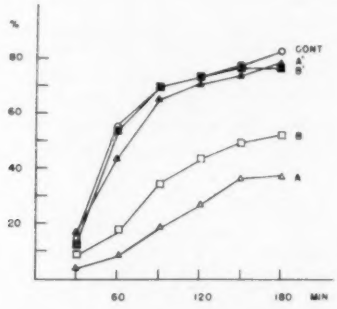

Fig. 3. — *Antidiuretic effects (Burn test) Each curve represents the mean value of 100 rats injected intraperitoneally with 1 ml of:*
A: *pregnant woman serum kept at low temperature.*
A': *pregnant woman serum dialyzed.*
B: *non pregnant woman serum kept at low temperature.*
B': *non pregnant woman serum dialyzed.*
Cont: *NaCl solution 0.9 per cent.*

means of the Burn test, is much greater than that of non pregnant women. Such a difference is striking because it was proved, using the same test, that the serum from pregnant woman has an antidiuretase activity much greater than that of the non pregnant serum. If the effects obtained with pregnant and non pregnant sera are compared, it is evident that the rate of destruction of the substance responsible for this antidiuretic activity is similar in both cases. These apparently paradoxical facts may be explained in different ways: a) the antidiuretic activity of serum is due to a substance other than the neurohypophyseal hormone used to prove the antidiuretase activity by Croxatto et al. (1953), and b) the hormone contained in the serum and that which causes the antidiuretic activity in the rat is the same, but is in a different state and protected from the inactivator enzyme. Incubation (enzymatic action?) or dialysis could be responsible in both cases for the disappearance of the substance from the serum. According to this hypothesis Croxatto et al. (1953) concluded that blood serum contains either several antidiuretic substances or only one, but in different forms.

Besides the free hormone, which would be rapidly destroyed by antidiuretase — specially in the pregnant cases — there would be two other substances of a very similar nature to the known hormone: one would be binded to blood proteins, from it could be progressively liberated and only then be exposed to inactivation; incubation and dialysis might favour the liberation of this fraction. A third antidiuretic fraction would be a polypeptide produced by deep hydrolysis of proteins.

The existence of an antidiuretic substance, whether different or not from the posterior pituitary hormone, but protected from the enzymatic activity of serum, would explain why there are no abnormal signs of diabetes insipidus in pregnant women, who have such a high capacity to inactivate vasopressin.

Parallel evidence has been reported by Vargas at al. (1949) on the oxytocic action. The oxytocic activity of pregnant women serum, tested *in vitro*, does not disappear as rapidly as when the hormone is added to the serum sample. However, their results differ from ours in that they found that the pregnant woman serum has less oxytocic potency than the non pregnant serum, although at the end of pregnancy this power is greater than at the beginning.

Conclusions

The antidiuretic activity of blood sera from pregnant women in the 9th month tested by means of the Burn test is higher than that of sera samples from non pregnant women.

Incubation of the sera at 37°C during 4 or 8 hours causes this antidiuretic activity to diminish progressively in both kinds of sera.

Dialysis, through a celullose membrane, and against current water (24 hours) causes an almost complete loss of the antidiuretic activity in both sera.

When this investigation had been finished, Hawker (1952) published his results, showing that the serum-antidiuretic-substance level is higher during pregnancy than during the menstrual cycle.

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EFFECTS OF bis-(8'quinoliloxy) 1,5-pentane di-iodoethylate (3381 RP) ON NEUROMUSCULAR SYNAPSE *

F. HUIDOBRO AND G. UGARTE

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SINCE CURARE and one of its alkaloids, *d*-tubocurarine (dTC), became introduced in clinic, many other compounds capable of producing neuromuscular paralysis have been synthesized. Notwithstanding, only the mechanism of action of dTC, decamethonium (C - 10) and succinylcholine is precisely known. The former (dTC) substance prevents the depolarizing effect of the chemical transmissor and the last two produce depolarization of the end-plate ([7], [14], [22]). This fact explains why compounds which antagonize the block induced by dTC may act quite differently on the block produced by C - 10 ([8]) and one may assume that compounds causing paralysis of the end-plate by mechanisms analogous to that of dTC should be antagonized in the same way as occurs with dTC; those behaving as C - 10, should be counteracted by the same substances.

A previous study demonstrated that neuromuscular paralysis produced by bis-(8'-quinolyloxy) 1, 5-pentane di-iodoethylate may be restored by several compounds quite differently than when these compounds act in front of dTC or C-10 ([8]). According to this assumption it could be assumed that the mechanism of neuromuscular block induced by 3381 RP is other than: a) the prevention of the depolarizing effect of the chemical transmissor, and b) the production of a depolarization at the end-plate level.

The purpose of this work has been to study the effect of 3381 RP in order to know if, as was assumed, this substance can provoke a neuromuscular paralysis through a synaptic blocking mechanism different to those hitherto known.

* This study was carried out under support of the Gildemeister Foundation, Santiago de Chile.

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As the aforementioned study (*) permits to conclude that Flaxedil and bis-(2'-dimethylamino-phenoxy)-1,5-pentane di-iodomethylate (3565 RP) have a similar effect to dTC, other experiments have been made to reinforce this possibility.

Material and methods

Non-selected adult cats were employed, preferently anesthetized with chloralose: 80 mg per kg of weight, injected into the femoral vein. Some of the animals were under sodium pentobarbital anesthesia (Nembutal "Abbott"), 0.33 g per kg of weight intraperitoneally.

Experiments were performed almost exclusively using the femoral quadriceps and only exceptionally the tibialis anterior muscle. Both were stimulated either indirectly through the nerve or directly. Previous aseptic section of the nerve was performed 6 to 12 days before the experiment. Condenser discharges were employed as stimuli, controlling their frequency by means of electronic valves. When the muscle was indirectly stimulated, the condensers time of discharge was 0.13 ms rising up to 3 ms when the muscle was directly stimulated. In both cases, stimuli were maximal.

The distal tendons of the muscles were isolated and muscular contractions were isometrically recorded in a smoked drum. Bones were fixed with steel nails. When the muscle was directly stimulated, steel needles were employed as electrodes; one inserted into the muscular mass and the other into the corresponding tendon. In cases of indirect stimulation, a silver electrode (isolated with rubber) was connected to the nerve centrally crushed. The frequency of stimulation was generally 17 per minute, but higher frequencies were also employed as will be mentioned later. A cannula was inserted into the trachea to permit artificial respiration when necessary.

A series of experiments was carried out on the (rectus anterior) muscle of *Bufo spinulosus* (chilean toad). The preparation was suspended in a 20 cc bath, in Tyrode solution bubbled with air. Isometric recording was performed.

The drugs employed were:

3381 RP - bis - (8'-quinolyloxy) 1,5 pentane di - iodoethylate (Rhone-Poulenc); at a dosis of 25 μg to 4 mg.

3565 RP - bis-(2'-dimethylamino-phenoxy)-1,5-pentane di-iodomethylate (Rhone-Poulenc); at a dosis of 0,5 to 1,5 mg.

Flaxedil-tris (triethylamino ethoxy) 1, 2, 3 benzene triiodoethylate (Rhone-Poulenc); at a dosis of 0,5 tol mg.

d-tubocurarine chloride at a dosis of 0,15 to to 0.45 mg.

Decamethonium bromide (C-10, Burroughs Wellcome and Co), at a dosis of 5 to 100 μg.

Acetylcholine chloride (Hoffman-La Roche) at a dosis of 20 to 60 μg.

Drugs were diluted in distilled water and injected into the terminal part of the abdominal aorta, after ligature of the inferior mesenteric, sacralis media and contralateral iliac arteries. They were rapidly injected

in a volume not exceeding 0.30 cc, with exception of 3381 RP which was diluted in a larger colume due to its low solubility. When several drugs were injected into the same animal the interval of time between injections was such as to allow the compounds to be eliminated or metabolized.

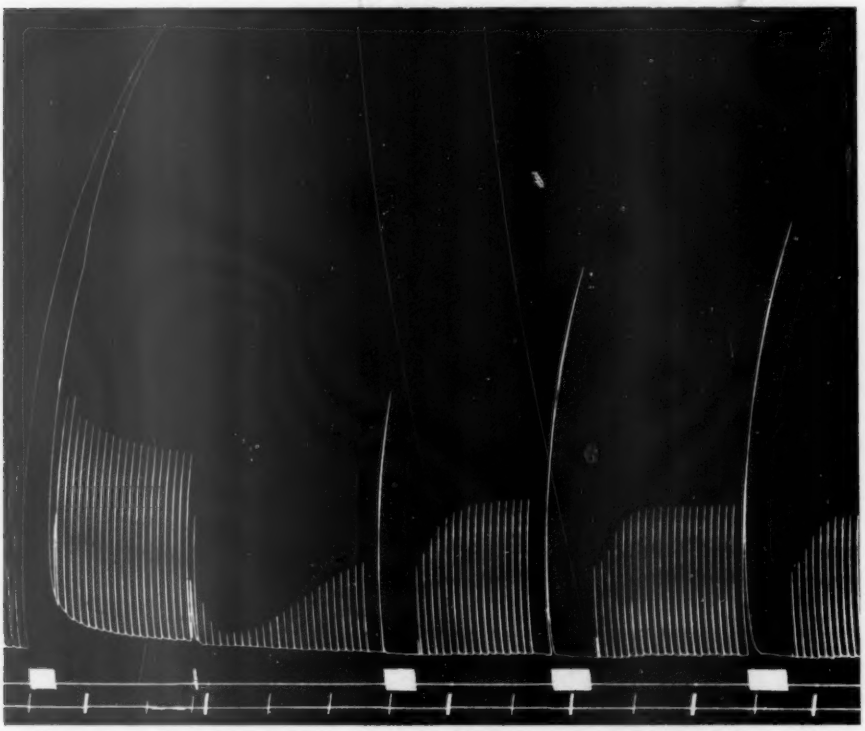

FIG. 1. — *Effect of 3381 RP on tetanus and post-tetanic twitching.*
Cat weighing 3.350 g-under chloralose anesthesia.
Quadriceps muscle stimulated through the nerve at a frequency of 17 per minute. At thick marks and during 15 seconds, frequency was changed to another of 71 stimuli per second. At thin marks, 2 mg of 3381 RP.
Time each 30 seconds.
(Deflection of the curve at the moment of 3381 RP injection is due to a mechanical artefact).

RESULTS

1 — *Influence of 3381 RP on muscular contraction produced by stimulus through the nerve.*

Compound 3381 RP injected during indirect stimulation of the

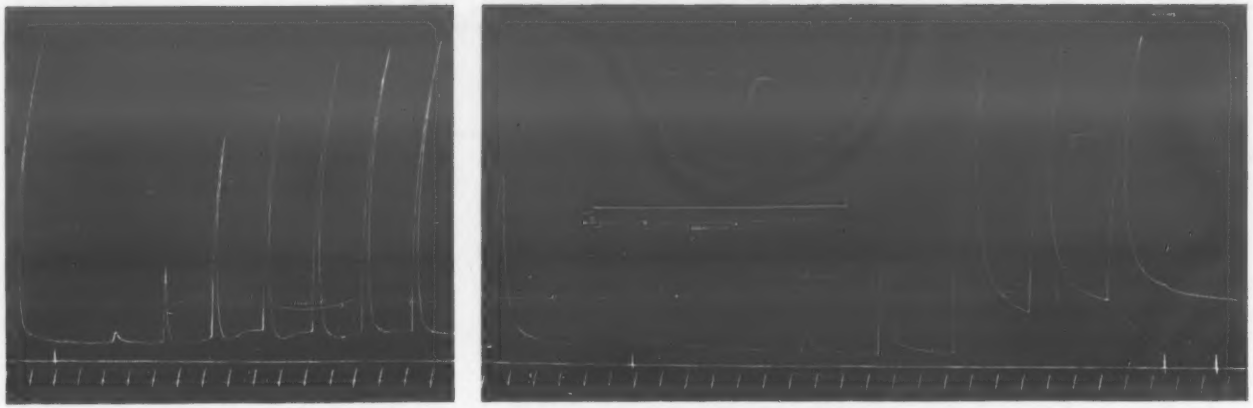

FIG. 2. — *Inhibitory effect of 3381 RP on muscular shortening induced by acetylcholine and decamethonium.*
Cat weighing 3.150 g, under chloralose anesthesia.
Quadriceps muscle denervated 7 days before.
At the left: muscular shortening induced by 20 μg of acetylcholine injected every 2 minutes. The mark indicates 0,75 mg of 3381 RP.
At the right: (the same animal) muscular shortening induced by 25 μg of C-10 injected every 3 minutes. At the first mark: 0,5 mg of 3381 RP.
At the last two marks: 0,5 and 1 mg, respectively, of 3381 RP. Time in minutes.

quadriceps, at a frequency of 17 per minute, causes depression of muscular twitching of an intensity and duration proportional to the dosis employed. It has an extremely short effect: paralysis appears almost instantaneously followed by a rapid recovery (fig. 1 and 7).

When the drug is given during direct muscular excitation produced by higher frequency of stimuli (5 to 15 per second), a depression of muscular twitching is observed accompanied by a decrease of the tension developed. If injected before stimulation, the characteristics of tetanus

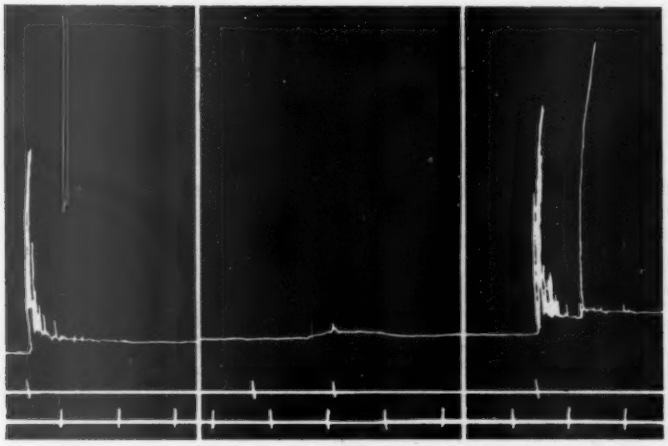

FIG. 3. — *Suppression of muscular shortening and of fasciculation produced by C-10 due to the effect of 3381 RP.*
Cat weighing 2.450 g, under chloralose anesthesia.
Normal quadriceps muscle.
At the left: at mark, injection in the abdominal aorta of 25 µg of C-10.
At the middle: at the first mark, 0.40 mg of 3381 RP; at the second, 25 µg of C-10.
At the right: at mark, injection of 25 µg of C-10.
Between the first and second figure, 10 minutes and between the second and the third, 15 minutes.
Time in minutes.

are the same as those existing before administration while the height of muscular shortening is lower compared with the control.

At a higher frequency of stimulation (50 to 74 stimuli per second) and the substance being administered before excitation, the height of contraction is small and followed by a rapid fatigue (fig. 1).

When short tetanus are alternated with a series of muscular twitches produced by stimuli of low frequency, muscular twitching subsequent to tetanization develop higher tension than that existing before tetanic stimulation ([4], [6], [9]). This after tetanus potentiation is markedly modified

by 3381 RP. As can be seen in fig. 1, post-tetanic twitching is deeply depressed by the action of the drug.

With the doses employed no muscular shortening was observed when 3381 RP was used during indirect muscular stimulation.

2 — *Effect of* 3381 *RP on denervated muscles.*

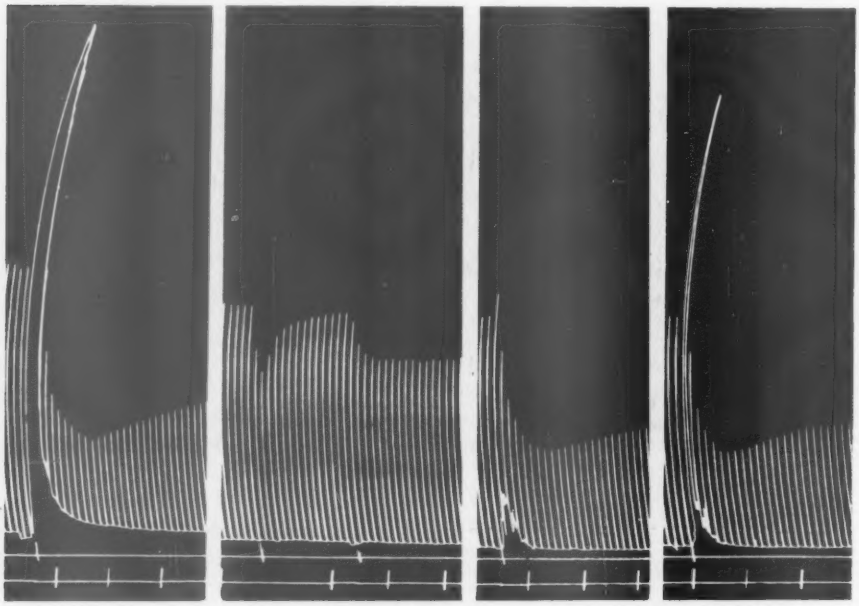

FIG. 4. — *Antagonisms between 3381 RP and C-10.*
Cat weighing 2.300 g under chloralose anesthesia.
Quadriceps muscle stimulated through the nerve at a frequency of 17 per minute.
First fig: at mark 7.5 μg of C-10.
Second fig.: (14 minutes after the first); first mark, 0,20 mg of 3381 RP; second mark, 7.5 μg of C-10.
Third fig.: (13 minutes after the second); at mark, 7,5 μg of C-10.
Fourth fig.: (45 minutes after the third); at mark, 7,5 μg of C-10.
Time every 30 seconds.

A) *Stimulated by electric currents.* — As no reference could be found in the consulted literature as to whether this compound depresses or not the muscular contraction induced by direct stimuli we investigated the problem under different experimental conditions. The substance was injected in: a) animals whose muscles had been previously denervated (6 to 12 days before) and directly stimulated, and, b) animals under large doses of curare whose muscles were directly stimulated. In none

of these two cases did RP 3381 cause a depression of muscular contractions.

B) *Stimulated by drugs.* — When the denervated muscle is excited by intraarterial acetylcholine injections, a shortening can be observed. Repeated injections with the same dose and every 2 to 3 minutes, provoke similar muscular shortenings. Once they are obtained, administration of 3381 RP reduces or causes the disappearance of muscular shortening, as

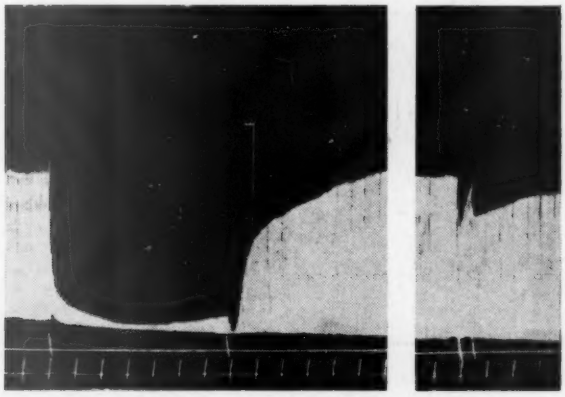

FIG. 5. — *Antagonism between C-10 and 3381 RP.*
Cat weighing 2.100 g under chloralose anesthesia.
Quadriceps muscle stimulated through the nerve at a frequency of 17 stimuli per minute.
At the left: first mark, 75 µg of C-10; second mark, 0.20 mg of 3381 RP.
At the right: (the same animal); first mark, 1 mg of 3381 RP; second mark, 75 µg of C-10.
Time in minutes.

may be seen in fig. 2, illustrating a typical experiment and showing the slow and gradual recovery. Contracture of denervated muscles is produced by acetylcholine ([5], [20]). The kymographic characters of this contracture are not modified by 3381 RP.

Compound 3381 RP affects the action of C-10 in the same way as that of acetylcholine. When muscular shortenings of the same amplitude have been obtained by means of C-10 intraaortic injections, compound 3381 RP may cause them to disappear completely for some time (fig. 2). Recovery is gradual and, occasionally, the muscular shortening may reach higher values than the control (fig. 2).

Compound C-10 produces muscular contractures ([21]). Fig. 2 shows that 3381 RP does not modify the C-10 induced contracture's kymographic characteristics (dTC acts the same as 3381 RP in this respect).

No shortening of denervated muscles is observed by administration

of 3381 RP when injected into abdominal aorta, whatever the dosis employed.

3 — *Effect of* 3381 *RP on drugs blocking neuromuscular synapses*

a) *Antagonism between* 3381 *RP and C*-10. — Compound C-10 can provoke on the skeletal muscles of cats under chloralose anesthesia, a contraction, a potentiation of muscular twitching, fasciculation pheno-

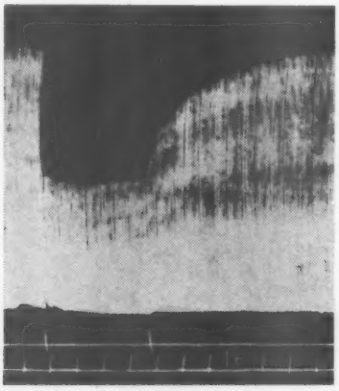

FIG. 6. — *Antagonistic effect of 3381 RP towards the paralyzing effect of C-10.*
Cat weighing 2.500 g under chloralose anesthesia.
Quadriceps muscle stimulated through the nerve at a frequency of 17 per minute.
First mark: 75 µg of C-10; second mark, 0.15 mg of 3381 RP.
Time in minutes.

mena and blocking of muscular contraction ([10], [16], [21]). All these phenomena may be abolished by the action of 3381 RP. Zaimis ([21]) demonstrated that small doses of C-10 produce muscular shortening accompanied by fasciculation. As can be seen in fig. 3, 3381 RP prevents apparition of the mentioned effects of C-10. On certain occasions, decamethonium before causing neuromuscular paralysis, induces a contraction of importance and certain duration, accompanied by intense electrical activity ([10]). Our present paper confirms the described phenomena. Fig. 4 represents kymographic recording of the mentioned facts and illustrates, in addition, that 3381 RP completely abolishes this effect. Since the simultaneous publication of Barlow and Ing ([1]) and Paton and Zaimis ([15]), it is well known that C-10 provokes neuromuscular paralysis. The paralyzing action of C-10 becomes markedly weakened if 3381 RP is previously given. This anti-C-10 effect can be seen in figs. 4 and 5.

dTC also prevents the potentiation of muscular twitching and the muscular shortening induced by C-10.

Compound 3381 RP can suppress neuromuscular block induced by C-10. This antagonic effect to C-10 may be preceded by a small and very

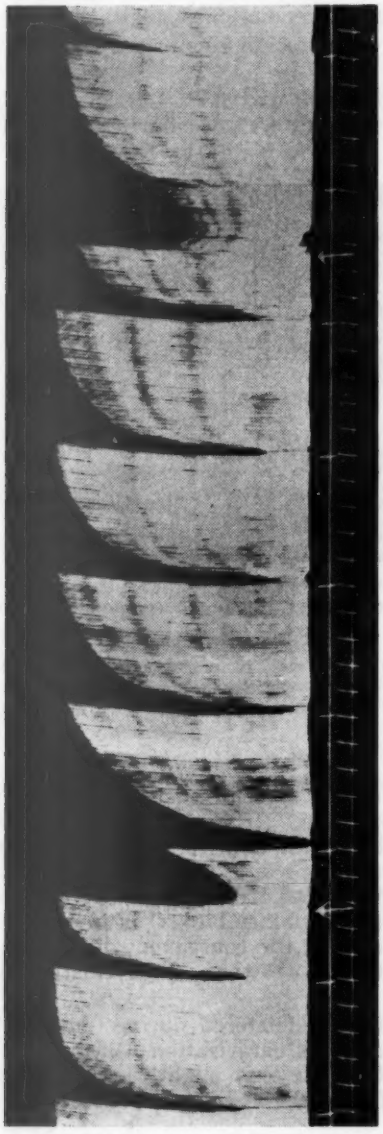

FIG. 7. — *Synergism between d-tubocurarine and 3381 RP; antagonism between C-10 and 3381 RP.*
Cat weighing 2.850 g. under chloralose anesthesia.
Quadriceps muscle indirectly stimulated at a frequency of 17 stimuli per minute.
At marks: 0.50 mg of 3381 RP.
First arrow: 0.15 mg of d-tubocurarine.
Second arrow: 75 μg of C-10.
Time in minutes.

short depression of muscle twitching, as shows in fig. 5. But as can be seen in fig 6, it is also possible to obtain recovery of muscular twitching depressed by C-10 without the aforementioned slight depression.

On the other hand C-10 is unable to counteract the paralysis produced by 3381 RP.

b) *Synergism between 3381 RP and dTC.* — If 3381 RP is injected in an amount sufficient to block indirect muscular stimulation at a fre-

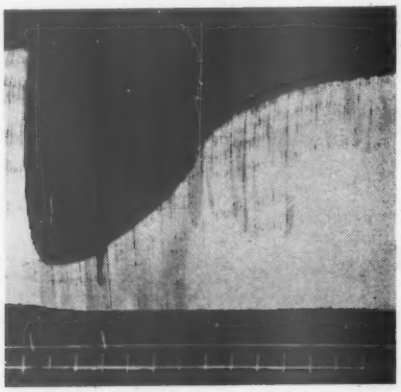

FIG. 8. — *3381 RP does not modify the course of spontaneous decurarization induced by d-tubocurarine.*
Cat weighing 2.100 g under chloralose anesthesia.
Quadriceps muscle indirectly stimulated at a frequency of 17 per minute.
First mark: 0.30 mg of d-tubocurarine.
Second mark: 0.20 mg of 3381 RP.
Time in minutes.

quency of 17 per minute and, during muscular depression or immediately after it, dTC is given, compound 3381 RP does not modify the blocking effect of dTC. Notwithstanding, with a different procedure it can be observed that dTC increases the depressor effect of 3381 RP. Repeated administration of the same doses of the drug, every 4 to 5 minutes, causes similar depression of muscular twitching. If dTC is injected previously to a new administration of the drug, the consequent depressions induced by 3381 RP are slightly more intense than those existing before the injection of dTC (fig. 7).

On the contrary, 3381 RP administered during curarization produced by dTC slightly increases this curarization. During the period of spontaneous decurarization, 3381 RP can slightly depress the muscle twitching, but does not modify at all the course of decurarization (fig. 8).

4 — *Effect of 3381 RP on the rectus anterior of the toad.*

The compound added at doses between 5 μg and 4 mg to the bath

containing Tyrode solution where the rectus anterior muscle of the toad is suspended, does not produce shortening of the muscle.

5 — *Effect of Flaxedil and* 3565 *RP on block induced by* 3381 *RP.*

A procedure similar to that described under 3 was followed; e. g. every 4 to 5 minutes equal doses of 3381 RP were administered. Previously to a new dosis, Flaxedil or 3565 RP were given. Under these conditions, the depressor effect of 3381 RP is exaggerated and pro-

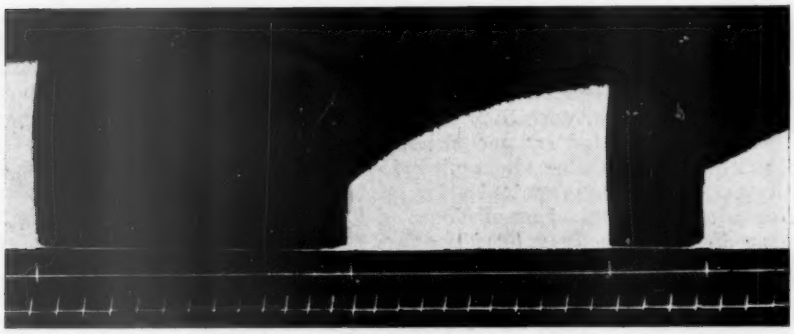

FIG. 9. — *Recovery of neuromuscular paralysis induced by 3565 RP and Flaxedil due to the effect of C-10.*
Cat weighing 1.750 g under Nembutal anesthesia.
Quadriceps muscle stimulated through the nerve at a frequency of 17 per minute.
First mark: 0.5 mg of 3565 RP.
Second and Fourth mark: 25 µg of C-10.
Third mark: 0.5 mg of Flaxedil.
Time in minutes.

longed. It may be said that these drugs have a similar effect as dTC although somewhat more intense.

6 — *Effect of C-10 on block induced by Flaxedil and* 3565 *RP.*

As the literature records data indicating that Flaxedil has a dTC like activity ([8], [18], [19]) and as in previous work we suspected that Flaxedil and 3565 RP behaved similarly and that their mechanism of action was the same as that of dTC ([8]), we only carried out the following type of experiments. A doses of Flaxedil or 3565 RP causing complete abolishment of muscular twitching was injected. When these reappeared, 25 µg of C-10 were given. A remarkable and important muscular recovery (fig. 9) was observed in every case immediately after the C-10 injection.

DISCUSSION

Considering that the nerve action potentials are not modified ([6]) and that no depression of muscular contraction induced by direct stimuli

exists, the effect of 3381 RP must be exerted at the neuromuscular synapse level.

The findings mentioned under "Results" seem to be clear enough for disregarding the possibility that 3381 RP may have a mechanism of action similar to C-10 (for references on the action of C-10, see: [10], [11], [12], [16], [21]). Moreover, this assumption ([8]) is reinforced by the lack of ability of the compounds such as: Ro 2-2561, Ro 2-2650, caffein and methrazol to counteract the paralysis provoked by the mentioned substance, while veratrine, 2, 4-D and nicotine do antagonize this paralysis.

In view that 3381 RP and dTC always produce an intense Wedenski effect, a depression of muscular twitching and no shortening of the muscle nor alteration in the twitching when the muscle was directly stimulated ([13]), it may be assumed that a certain similarity exists between both compounds. Furthermore they both depress the shortening of the denervated muscle excited by acetylcholine ([6]) and C-10, they prevent the apparition of muscular shortening induced by C-10 in normal muscles and the apparition of potentiation of the muscular twitching observed after administration of small doses of C-10 and they decrease the paralyzing effect of the drug ([16]). The fact that dTC may increase the action of 3381 RP would reinforce this analogy.

Nevertheless, this resemblance does not resist a careful analysis ([10], [11], [16]) since 1) 3381 RP may antagonize the effect of C-10; 2) it would be difficult to explain that this substance does not markedly modify the action of dTC, and 3) because the action of this last drug decreases after administration of the quinolinic derivative without counteracting the blocking effect of 3381 RP. Similarly the fact that methrazol, caffein, neostigmine, potassium chloride, Ro 2-2561 and Ro 2-2650 do not antagonize the depressor effect of 3381 RP, as they do with regard to dTC ([8]), would lead to the conclusion that there may be several mechanisms of action. Other differences also exist; dTC produces a post tetanic decurarization ([13]) while post tetanic muscular twitching is depressed when 3381 RP is used. Furthermore, dTC does not prevent muscular fasciculation produced by C-10 ([16]) as occurs with 3381 RP. Hence, it could be assumed that the effect of the compound extends further than the end plate, a fact which has not been described for the alkaloid of curare.

It could be argued that 3381 RP blocks neuromuscular synapses due to its anti-cholinesterase activity ([2]). But this does not seem to be the case, since apart from depressing the after tetanus increase ([17]), no decurarizing properties, characteristic of anti-cholinesterase substances have been described for this substance.

If the action of 3381 RP cannot be explained by a depolarization of the end-plate zone nor by the prevention of depolarization of the transmissor nor by causing paralysis by the double mechanism mentioned by Zaimis ([23]), another mechanism of action must be suggested. We merely suggest that it may be a polarizer of the end-plate, a hypothesis which would explain its actions.

It has been suggested that the decurarizing action of C-10 in front of the paralysis produced by dTC should be expected in view of the

mechanism action of both drugs ([11]). The fact that C-10 antagonizes muscular block produced by 3565 RP and Flaxedil, is another argument in favor of the idea that the paralyzing mechanisms of dTC, 3565 RP and Flaxedil may be analogous. This hypothesis becomes stronger when considering the fact that these three drugs behave similarly in front of the block induced by 3381 RP.

SUMMARY

1) Neuromuscular paralysis induced by 3381 RP has been investigated in cats under chloralose anesthesia, the following facts having been observed:

The substance produces depression of muscular twitching when the quadriceps is stimulated through the nerve; it produces intense Wedenski and depresses post-tetanus twitching.

It depresses muscular shortening induced by acetylcholine and decamethonium in denervated muscles and does not alter the contraction provoked by direct stimuli, either in denervated muscles or in normal muscles of animals which have been given large doses of d-tubocurarine.

It does not produce contraction of the normal or denervated muscle of the cat or of the rectus anterior of the toad.

It prevents the apparition of potentiation of muscular twitching, muscular contraction and fasciculation produced by decamethonium and partially prevents the paralysis induced by C-10. Decamethonium antagonizes neuromuscular block induced by 3381 RP.

3381 RP does not potentiate the action of d-tubocurarine.

2) It has been observed that in cats under sodium pentobarbital anesthesia, decamethonium may antagonize neuromuscular paralysis induced by Flaxedil and 3565 RP and that both drugs potentiate the response of 3381 RP.

The mechanism of neuromuscular paralysis induced by the three drugs has been discussed, suggesting the hypothesis that 3381 RP may act as polarizer of the end-plate.

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CHANGES IN BLOOD SUGAR AND SERUM INORGANIC PHOSPHORUS AFTER DEXTROSE OR INSULIN ADMINISTRATION IN PREGNANCY

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AS EARLY as 1912, Schirokauer pointed out the frequent occurrence of post prandial glycosuria in fourteen pregnant women [1].

Concerning the existence of a diminished glucose tolerance in pregnancy, opinions have been divided. Some [2, 3], find no difference between non-pregnant and pregnant women, while others [4, 5, 6, 7, 8] report a diminished glucose tolerance test in this condition.

In view of these contradictions, we decided to re-investigate the problem, applying the "Delta G/ Delta P test" described by one of us [15], in which the changes in serum inorganic phosphorus as well as those in blood sugar following an intravenous injection of dextrose are measured. Finally, a number of intravenous insulin tests were carried out.

The decrease in serum inorganic phosphorus which follows dextrose administration has been known for some time [9, 10]. Such a decrease does not take place in pancreatectomized animals [11] and has been proposed as a help in the diagnosis of diabetes mellitus [12, 13, 14, 15], etc. It does occur however in a certain percentage of diabetics patients with blood sugar under 250 mg 100 ml, and it has been suggested that it reveals insulin production [16].

The administration of insulin in normal or panereatectomized animals and diabetic patients induces the fall in inorganic phosphorus [17, 9, 18, 19, 20, 21, 22], etc.

MATERIAL AND METHODS

The "Delta G/ Delta P test" [15], was performed in 28 normal preg-

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* Maternidad Concepción Palacios.

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TABLE I

Means and standard errors of the changes in blood sugar and serum inorganic phosphorus after the intravenous injection of glucose (1 ml of 50 % sol/K of body weight).

		N° cases	minutes after the injection				
			Initial values	15'	30'	45'	60'
Blood Sugar mg/100 ml	Non pregnant	20	82±2.3	+87±5.6	+49±3.8	+20±3.4	+1 ±3.1
	Pregnant	28	64±1.7	+118±5.6	+69±4.0	+40±3.6	+17±3.2
"T" Values			6.30	—3.90	+3.60	—4.04	—3.60
Inorganic Phosphorus mg/100 ml	Non pregnant	20	4.07±0.12	—0.74±0.10	—0.77±0.14	—0.70±0.06	—0.59±0.08
	Pregnant	28	3.52±0.12	—0.38±0.07	—0.33±0.09	—0.46±0.07	—0.41±0.06
"T" Values			+3.20	—3.00	—2.60	—2.60	—1.80

nant women during the 7th to 9th month of pregnancy and in 20 normal non pregnant women of comparable age. After a half hour rest, 0.5g/kg of body weight of dextrose as a 50% solution was injected intravenously at a rate close to 10 ml minute. Blood sugar ([23]), and serum inorganic phosphorus ([24]) were measured in duplicate, in the fasting state and 15, 30, 45 and 60 minutes after the end of glucose administration. The insulin tests were carried out in exactly in the same way, except that insulin 0.1 units/kg of body weight was injected instead of glucose. Statistical analysis of the results was done with Fisher's "T" test. The limit of significance was taken as T = 2.

Results

The average of the fasting blood sugar and serum inorganic phosphorus and the differences between initial values at 15, 30, 45 and 60 minutes after the injection are shown in tables I (after glucose) and II (after insulin).

Discussion

The fasting blood sugar is distinctly lower in the pregnant group. Ten of the cases had truly hypoglycemic levels (less than 60 mg/ 100 ml)

TABLE II

Means and standard errors of the changes in blood sugar and serum inorganic phosphate after the intravenous injection of insulin (0.1 U/K of body weight)

		N° cases	minutes after the injection				
			Initial values	15'	30'	45'	60'
Blood Sugar mg/100 ml	Non pregnant	37	75±1.34	—40±2.00	—44±2.02	—32±2.61	—16±2.20
	Pregnant	19	69±2.91	—17±2.25	—23±2.41	—16±2.19	— 7±1.70
"T" Values			1.90	—7.64	—6.70	—5.90	—3.23
Serum Inorganic Phosphorus mg/100 ml	Non pregnant	37	3.55±0.08	—0.56±0.06	—0.96±0.07	—1.12±0.04	—0.84±0.06
	Pregnant	19	3.67±0.14	—0.28±0.05	—0.33±0.06	—0.38±0.11	—0.19±0.10
"T" Values			0.92	—3.58	—6.80	—6.33	—3.50

Those findings are in essential agreement with those of Rowe et al [26] although the difference between the normal and pregnant groups in Rowe's patients was less marked.

Other authors report normal fasting blood sugar in pregnancy [2, 27, 28].

The average fasting serum inorganic phosphorus was also lower in the pregnant group, although here the difference was not as striking. 21% of our cases showed values between 1.50 and 3.00 mg/100 ml where as in the control group only 5% showed similar values.

Glucose tolerance, *as measured by the subject's ability to remove the injected glucose from the blood stream* ("Delta G"), was distinctly and significantly lowered in the pregnant group. 17% of the cases showed a rise in blood sugar of more than 50 mg/100 ml 45 minutes after the injection of glucose, a value which in a non-pregnant individual would strongly suggest the diagnosis of diabetes. [15]. None of the normal women showed this phenomenon. Labbé and Chevki, in 53 pregnant women, found high and prolonged blood sugar curves after the oral administration of glucose [4]. Bokelman and Rotter had even proposed this diminished tolerance as a test for pregnancy [5]. Similarly, Williams and Welles [6], Hurwitt and Jensen [7] and Richardson and Bitter [8] found a diminished glucose tolerance in a certain percentage of pregnant women.

On the other hand, Elias et al [2], and Johnson and Bonsnes [3] report normal sugar tolerance in pregnancy following intravenous administration of glucose. If the figures of the latter authors are scrutinized, however, it is clear that the pregnant group shows a lower initial value and a greater differential rise in blood sugar. Since the initial value in the pregnant group is abnormally low, it appears to us important to consider the *changes* in blood sugar rather than the absolute values, in order to make clear the reduced glucose tolerance in this condition.

The decrease in serum inorganic phosphorus is distinctly less in the pregnant group as compared with the control group. 34% of the pregnant women showed changes of less than 0.30 mg/100 ml, at 45 minutes, which is the limit value in normal cases [15], whereas none of the normal controls showed decreases of less than 0.30 mg/100 ml. This defect in the serum inorganic phosphorus changes was found in 69% of 54 diabetics patients [16] and could be attributed to a defect in insulin production or to an inhibition of the action of insulin. In the present case, the latter mechanism would appear more likely, since the response of blood sugar and serum inorganic phosphorus to exogenous insulin is distinctly reduced in the pregnant group.

Summary

Changes in blood sugar and serum inorganic phosphorus were measured before and 15, 30, 45 and 60 minutes after the intravenous injection of dextrose (0.5 gm/kg of body weight) in a group of 28 women in the 7th to 9th month of pregnancy and a group of 20 non-pregnant women of comparable age. A similar study was performed after the intravenous injection of 0.1 units/kg of body weight of insulin in 19 pregnant women (7th to 9th month and in 37 non-pregnant women. A significantly greater increase in blood sugar and lesser decrease in serum inorganic phosphorus following dextrose were found in the pregnant group.

The blood sugar and serum inorganic phosphorus fall was significantly lesser in the pregnant group following insulin, as compared with the non-pregnant group.

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GLUCOSE, INSULIN AND EPINEPHRINE TOLERANCE TESTS IN THE NORMAL AND HYPOPHYSECTOMIZED TURTLE "PSEUDEMYS D'ORBIGNYI" *

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THE HYPOGLYCEMIC effect of insulin is very slow in poikilotherms at ambient temperature, as was reported on *Bufo arenarum* and *Leptodactylus ocellatus* (Houssay, Sordelli and Mazzocco, 1923; Houssay & Rietti, 1924), on fishes (Houssay & Rietti, 1924; Mann, Bollman & Magath, 1924; Olmstedt, 1924; Root, Hall & Gray, 1931), on snakes (Houssay, Sordelli & Mazzocco, 1923; Houssay & Rietti, 1924; Prado, 1947) and on crocodiles (Coulson & Hernández, 1953).

In the turtle *Hydraspis hilarii* the blood glucose level rose at first, and did not fall for 5 1/2 hours (Houssay, Sordelli & Mazzocco, 1923); in the turtle *Graphtemys geographicus* the blood glucose level did not fall during the fist 6 to 8 hours, but there was hypoglycemia after 24 to 36 hours, which reached even lower levels after 60 to 96 hours (Mann, Bollman & Magath, 1924). Hypophysectomized toads had a greater hypoglycemic reaction to insulin than normals (Houssay, Mazzocco & Rietti, 1925). This reaction could be reduced by the injections of extracts of the hypophysis, particularly the *pars distalis* (Houssay & Potick, 1929).

The hyperglycemic effect of epinephrine is also prolonged in poikilotherms. The hyperglycemia lasted 40 to 50 hours both on *Bothrops jararaca* (Prado, 1947) and *Aligator mississipiensis* (Coulson & Hernández, 1953). Hypophysectomized toads (*Bufo arenarum*) had a smaller elevation of blood glucose after epinephrine than normals (Houssay & Di Benedetto, 1932; Houssay & Gerschman, 1947).

The following experiments were performed in order to study com-

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paratively the tolerance to glucose, insulin and epinephrine of normal and hypophysectomized turtles *Pseudemys d'Orbignyi.*

MATERIAL AND METHODS

The experiments were done during the month of July (middle winter) under a temperature of about 18°C ranging from 16° to 20°C; some complementary experiments were carried out in November (Spring). *Pseudemys d'Orbignyi* turtles of both sexes, weighing from 600 to

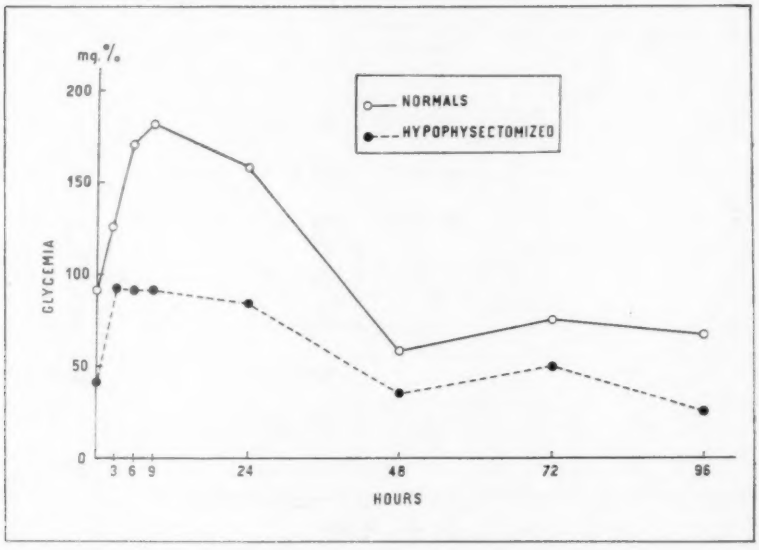

FIG. 1. — *Blood glucose levels after administration of 500 mg of glucose per kg, orally, in winter.*

1600 g the normals, and from 1500 to 2300 g the hypophysectomized, under 24 hours fasting, were used as experimental animals. They came from our vivarium, where they had stayed for four months.

Hypophysectomy was performed following the technique developed by one of the authors (Wagner, unpublished).

Tolerance tests were done as follows: glucose was administered orally as a 10 to 50 per cent solution in distilled water, by means of a fine catheter and in doses of 200, 500 and 1000 mg/kg to normal, and 500 mg/kg to hypophysectomized animals. Insulin* was injected subcutaneously in doses of 1, 2 or 4 U/kg to normal and 1 U/kg to hypophysectomized turtles. Epinephrine clorhydrate** was administered subcutaneously as a 1‰ solution in distilled water, in doses of 0.5, 1, 2 and 3 mg/kg

* Insulin Labor
** Adrenaline Geyer.

TABLE I

Glucose tolerance test of the turtle (Pseudemys d'Orbignyi) in July (winter). Averages

	Normal			Hypophysectomized
N° of animals	6	11	3	6
Glucose mg/kg	1.000	500	200	500
Blood glucose (mg per cent) (Hours)				
0	89 ± 7.5*	88 ± 8.1	73 ± 15.0	36 ± 5.6
3	199 ± 6.5	125 ± 14.8	150 ± 7.8	68 ± 3.0
6	180 ± 10.7	173 ± 13.7	138 ± 5.3	95 ± 15.0
9		182 ± 66.0		93 ± 13.7
24		159 ± 16.4	177 ± 34.7	88 ± 19.7
48		63 ± 21.7		38 ± 12.0
72		78 ± 17.5		51 ± 9.7
96		71 ± 4.4		24 ± 3.3
In the spring				
N° of animals		3		3
Blood glucose (mg per cent) (Hours)				
0		112 ± 31.4		82 ± 22.2
3		113 ± 20.2		97 ± 22.1
6		153 ± 17.9		137 ± 26.2
9		207 ± 20.0		65 ± 12.3
24		114 ± 17.8		61 ± 14.4
48		77 ± 15.3		73 ± 33.1
71		87 ± 15.5		61 ± 7.6

* Standard error of the mean.

to normals and 0.5 mg/kg to hypophysectomized turtles. In all cases blood samples were obtained at 0, 3, 6, 9, 24, 48, 72, and 96 hours.

Blood samples were obtained from the jugular vein after dissection followed by suture of the skin strip. Blood glucose determinations were made using the Somogy-Nelson method.

Serial extractions of blood, without the administration of any

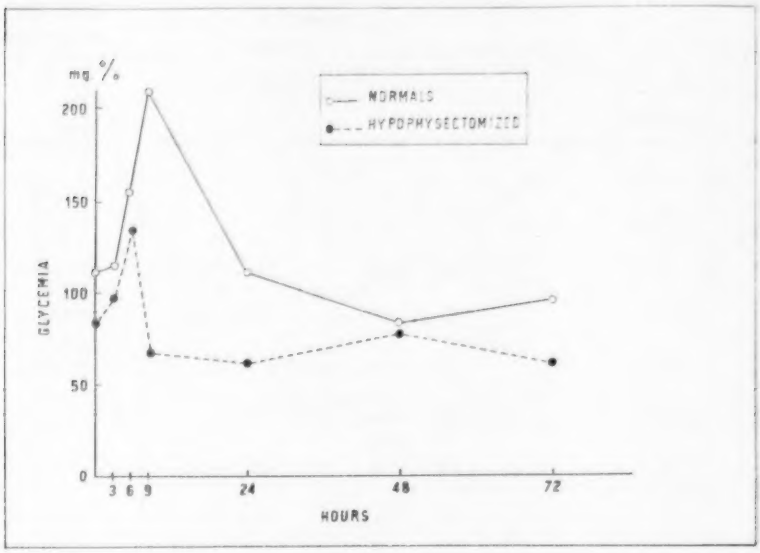

FIG. 2. — *Blood glucose levels after administration of 500 mg glucose per kg, orally, in spring.*

substance, were done in normal and hypophysectomized turtles in order to determine the influence of manipulation on the blood sugar level.

RESULTS

In Table I and Figure 1, the influence of different amounts of glucose on normal and hypophysectomized turtles is reported. There was a lower fasting level and a smaller rise of blood glucose level following glucose administration in hypophysectomized than in normal animals. In spring (fig. 2) the blood sugar rise and specially the consecutive fall were definitely more rapid than in winter.

The blood sugar curves of the insulin tolerance test (Table II and Figure 3) show a remarkable response in the hypophysectomized animals, in which, with a subcutaneous dose of 1 U/kg of insulin, there was a fall of the glycemia to 0 mg per cent in 24 hours without any objective

TABLE II

Effect of insulin on blood glucose of the turtle (Pseudemys d'Orbignyi) *in July (winter). Averages*

	Normal		Hypophysectomized
N° of animals	5	6	6
Doses U/kg	1	2	1
Blood glucose (Hours)			
0	84 ± 15.7*	91 ± 6.0	29 ± 2.0
3	83 ± 11.3	95 ± 34.2	31 ± 4.2
6	63 ± 11.5	67 ± 8.3	17 ± 4.5
9	53 ± 30.5		11 ± 2.3
24	28 ± 17.8	18 ± 14.2	0 ± 0
48	34 ± 11.0	26 ± 6.4	2 ± 0.7
72	62 ± 14.0	79 ± 20.5	29 ± 2.1
96	42 ± 36.0		26 ± 6.7

* Standard error of the mean.

symptoms of hypoglycemia. The blood sugar values took a long time to return to normal, in both normal and hypophysectomized turtles.

The administration of epinephrine to hypophysectomized turtles (Table III and Figure 4) produced a smaller and shorter rise of glycemia than in normals.

In both normal and hypophysectomized turtles, manipulation of tissue during the taking of blood samples produced only transitory and unimportant variations of blood glucose levels (Table IV).

Discussion

Our studies on the tolerance to glucose, insulin and epinephrine of both normal and hypophysectomized turtles *Pseudemys d'Orbignyi* were

performed during winter with a laboratory temperature of 18°C. ranging from 16°to 20°C. This fact is emphazised because of the known influence of temperature on this kind of experiments. Coulson & Hernández (1953), for instance, observed recently that the time needed for the blood glucose to return to the initial level, after glucose administra-

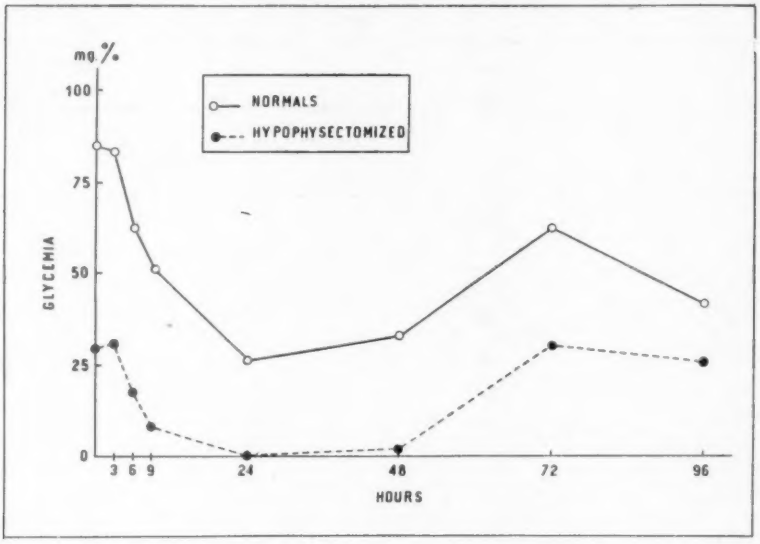

FIG. 3. — *Blood glucose levels after injection of 1 unit of insulin per kg, subcutaneously (posterior leg).*

tion, was 72 hours at 28°C and 180 hours at 16°C. In our experiments (fig. 1 and 2) a similar difference was found between winter and spring blood sugar curves. The return to initial level was remarkably rapid in the hypophysectomized turtles in spring. The curve obtained depends on speed of digestive absorption and speed of removal or utilization of the blood sugar during the experiment.

In agreement with results in other poikilothermal animals, the relative delay in restoration of blood glucose to initial levels is clearly shown in our tolerance curves. We think, with Leal Prado, that perhaps this "slow motion metabolism" in the turtle (Root, Hall & Gray, 1931) can be helpful in the study of certain nutritional aspects. Furthermore, it is an easy animal to handle, it is easily obtained, and it rapidly adapts itself to the captivity conditions of the vivarium. The response to glucose administration increased in speed and intensity with the doses; the optimal dose being, in our opinion, 500 mg/kg, because after 24 hours normal values of glycemia were restored. It is for this reason that this dose was selected to be administered to hypophysectomized turtles. When compared with normal turtles, there was a smaller elevation of blood

TABLE III

Effect of epinephrine on blood glucose of the turtle (Pseudemys d'Orbignyi) *in July (winter). Averages*

	Normal		Hypophysectomized
N° of animals	4	2	4
Doses mg/kg	0.5	1	0.5
Blood glucose (Hours)			
0	57 ± 20.6*	85 ± 45.0	82 ± 8.6
3	129 ± 16.6	151 ± 41.0	122 ± 13.7
6	174 ± 25.2	204 ± 50.0	107 ± 8.6
9	258 ± 28.0		192 ± 15.5
24	186 ± 34.7	288 ± 4.0	191 ± 28.6
48	150 ± 33.1	237 ± 125.0	105 ± 10.5
72	145 ± 45.8	247 ± 21.0	93 ± 14.4
96	170 ± 31.1	297 ± 35.0	62 ± 18.9

* Standard error of the mean.

sugar in the hypophysectomized turtle, probably as a result of the lack of the glycostatic function of the pituitary gland. It is possible that in the operated turtles, the rate of intestinal absorption is also slower, as has been observed in hypophysectomized rats.

The insulin curves showed a discrete rise of blood sugar during the first three hours; this was probably due to the presence of a hyperglycemic factor in the commercial insulin used, as previously pointed out by Houssay, Sordelli & Rietti (1923). It is important to note that after 24 hours the blood glucose values fell to zero (0 mg per cent) in all the hypophysectomized animals (1 U/kg) and also in several normal animals (2/3 U/kg), without any objective symptoms of hypoglycemia. This greater sensitivity of hypophysectomized turtles to insulin agrees with

the classical experiments performed by Houssay and coworkers in other species of animals.

Epinephrine produced a remarkable and sustained hyperglycemia, in normal turtles, which was present until the fourth day after its administration. This rise of the blood glucose levels was evident at the first hour after administration, a phenomenon that was not observed by Coulson & Hernández.

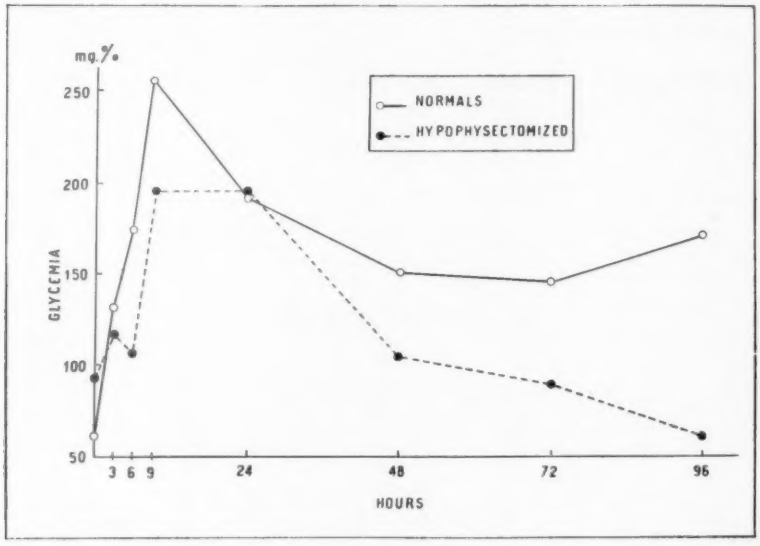

FIG. 4. — *Blood glucose after injection of 0.5 mg of L-epinephrine subcutaneously (posterior leg).*

In their experiments in alligator and caimán, epinephrine was given by means of intracardiac injection. In hypophysectomized turtles (0.5 mg/kg) the epinephrine hyperglycemia was less and shorter than that in normal ones. This lower hyperglycemia due to epinephrine in hypophysectomized animals is well known in mammals. That could be due to less glycogenolysis.

In these experiments, as in others now in course, an apparent shortening of the blood clotting time during the hyperglycemic period has been observed and it is unrelated to the cause of the hyperglycemia.

A group of normal turtles "without treatment" was subjected to the same number of blood extractions as the other group in order to determine if simple damage of tissue or emotional factors encountered during

TABLE IV

Blood glucose of control turtles "without treatment" in July (winter). Averages

	Normal	Hypophysectomized
N° of animals	12	2
Blood glucose (Hours)		
0	38 ± 6.0*	79 ± 1.0
3	56 ± 0	80 ± 39.5
6	85 ± 9.0	77 ± 27.0
9		107 ± 19.0
24	85 ± 9.0	60 ± 14.0
48	100 ± 12.0	72 ± 10.0
72	97 ± 15.0	69 ± 17.0
96		61 ± 3.0

* Standard error of the mean.

the taking of blood samples would have any effect on the blood glucose levels, as observed by Leal Prado (1946) and Britton & Kline (1939).

SUMMARY AND CONCLUSIONS

Tolerance to glucose, insulin and epinephrine was studied in normal and hypophysectomized turtles *Pseudemys d'Orbignyi*. In order to exclude the possibility of blood sugar level variations due to simple damage of tissues, control experiments were made with a group of normal animals, submited to jugular vein dissections and withdrawls of blood. The results obtained substantiate the following conclusions:

1) Restoration of blood glucose to initial values after administration of glucose, insulin or epinephrine, is a slow process.

2) Hypophysectomized turtles showed a remarkable sensitivity to

insulin, which caused blood glucose levels to fall to zero (0 mg per cent) after 24 hours in all the observations. Objective symptoms of hypoglycemia were not observed.

3) The administration of insulin produced hyperglycemia in normals during the first 24 hours. This may be related to contamination with a hyperglycemic factor in the commercial product employed.

4) After oral administration of glucose, blood sugar values reached higher levels in normal than in hypophysectomized turtles. The return to initial level was definitely more rapid in the hypophysectomized animals in spring.

5) Epinephrine produced a longer and greater hyperglycemia in normal than in hypophysectomized turtles.

6) Simple damage of tissues encountered during the taking of blood samples did not produce any considerable change of blood glucose levels in normal turtles.

We wish to thank Professor B. A. Houssay and Dr. R. R. Rodriguez for their scientific advice and inspiration.

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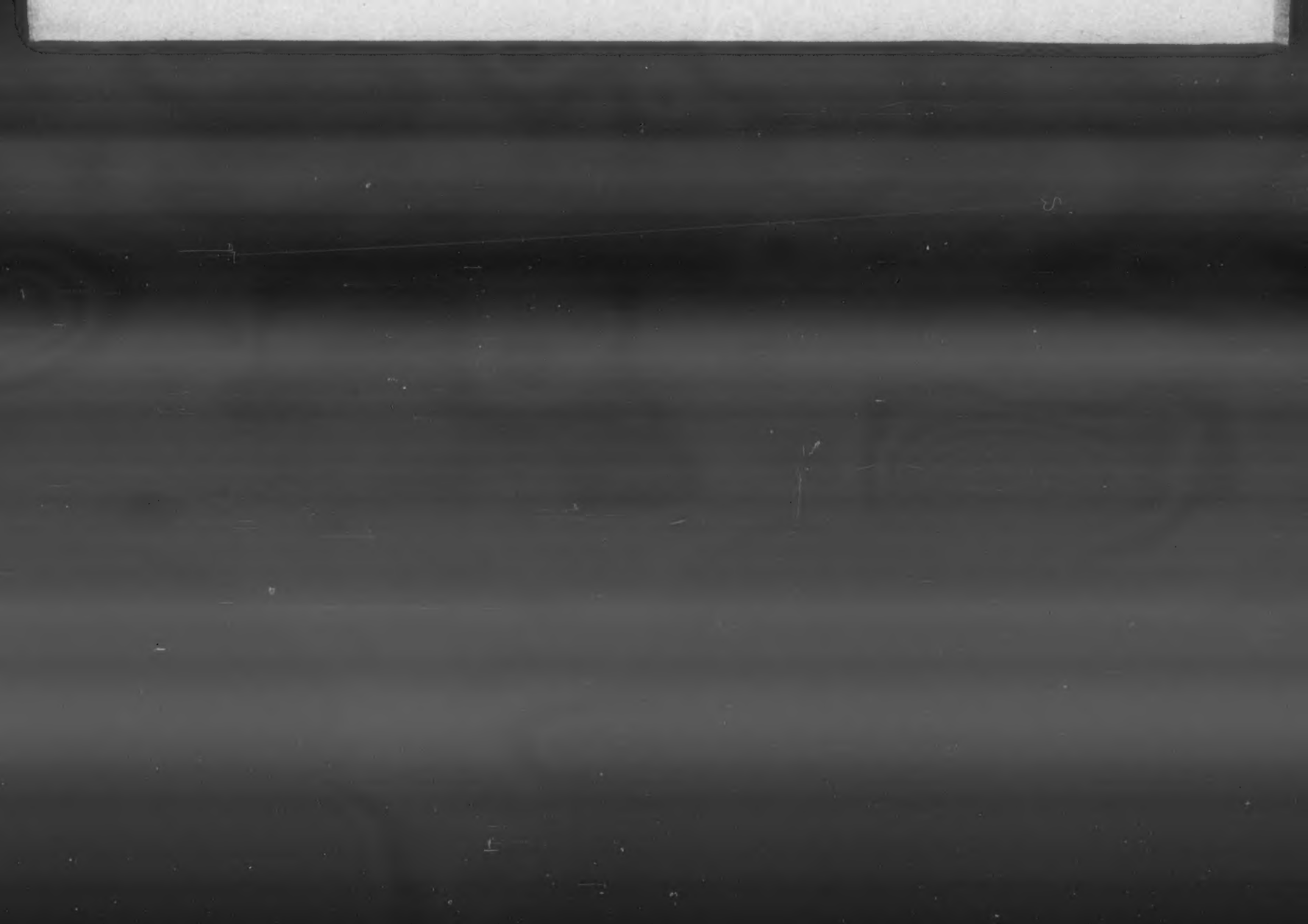

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centímetro	cm	centímetro cúbico	cm^3	gama	γ
milímetro	mm	mililitro	ml	por ciento	%
micrón	µ	kilogramo	kg	hora	h
milimicrón	mµ	gramo	g	minuto	m
Ansgtröm	Å	miligramo	mg	segundo	s
				milisegundo	ms

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